

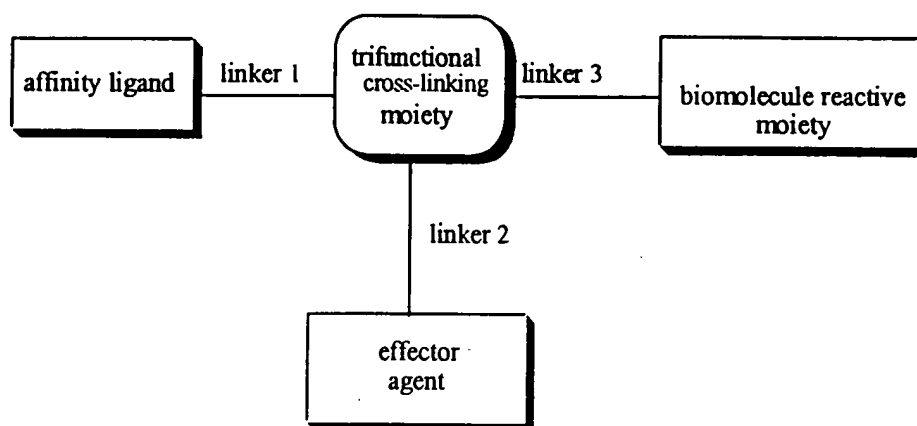
IN THE CLAIMS

Please amend Claims 33, 37, 55, 56, 64, 65, 70, 88 and 89 as shown in the following listing of claims.

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1.-32. (Withdrawn)

33. (Currently Amended) A single molecule reagent for conjugation to a biomolecule, provided with at least three functional parts, and corresponding to the following schematic structure (I) :



the single molecule reagent comprising:

a trifunctional cross-linking moiety, which is optionally tetrafunctional;

an affinity ligand, coupled to the trifunctional cross-linking moiety via a first linker which is optionally stabilized to inhibit enzymatic cleavage of the affinity ligand,

the affinity ligand having an affinity to bind specifically to at least one member selected from the group consisting of avidin; a ~~derivative, mutant or fragment~~ derivation of avidin having essentially the same binding function to the affinity ligand as avidin; streptavidin; and a ~~derivative, mutant or fragment~~ derivation of streptavidin having essentially the same

binding function to the affinity ligand as streptavidin, the chosen member exhibiting an affinity constant of at least  $10^6 \text{ M}^{-1}$  toward the affinity ligand;

an effector agent, coupled to the trifunctional cross-linking moiety by a covalent bond or by a second linker, the effector agent having an in vivo, ex vivo or in vitro effect on at least one member selected from the group consisting of a cell, a tissue, and a humoral molecule other than a biomolecule linked to the tri-functional cross-linking moiety, wherein the effector agent is selected from the group consisting of a synthetic or naturally occurring toxin; an enzyme, optionally ~~capable of~~ for converting a pro-drug to an active drug; a hormone; an immunosuppressive agent; an immuno-stimulating agent; a radionuclide binding/bonding moiety to which is optionally bound or chelated a radiosensitizer, an enhancer for an X-ray, MRI or ultrasound technique, or a non-radioactive element which can be converted to a radioactive element by means of external irradiation; a photoactive compound; a compound used in photoimaging; and a compound used in photodynamic therapy; and a biomolecule reactive moiety, coupled to the trifunctional cross-linking moiety, optionally via a third linker, the biomolecule reactive moiety being able to react with a biomolecule to form a covalent bond with the biomolecule.

34. (Previously Added) The single molecule reagent according to claim 33, wherein the trifunctional cross-linking moiety comprises a member selected from the group consisting of triaminobenzene, tricarboxybenzene, dicarboxyaniline and diaminobenzoic acid.

35. (Previously Added) The single molecule reagent according to claim 33, wherein the affinity ligand comprises biotin or a biotin derivative having essentially the same binding function to avidin or streptavidin as biotin.

36. (Previously Added) The single molecule reagent according to claim 33, wherein the affinity ligand comprises a biotin derivative selected from the group consisting of norbiotin, homobiotin, oxybiotin, iminobiotin, desthiobiotin, diaminobiotin, biotin sulfoxide, and biotin sulfone.

37. (Currently Amended) The single molecule reagent according to claim 33, wherein the affinity ligand comprises a biotin derivative which inhibits ~~biotinidase~~ biotinidase from enzymatically cleaving the biotinamide bond.

38. (Previously Added) The single molecule reagent according to claim 37, wherein the biotin derivative is selected from the group consisting of norbiotin and homobiotin.

39. (Previously Added) The single molecule reagent according to claim 35, wherein the first linker serves as a spacer between the trifunctional cross-linking moiety and the biotin moiety such that binding to the biotin moiety is not diminished by steric hindrance.

40. (Previously Added) The single molecule reagent according to claim 35, wherein the first linker comprises at least one member selected from the group consisting of compounds containing hydrogen-bonding atoms, and compounds containing ionizable groups, to thereby increase the water solubility of the biotin moiety.

41. (Previously Added) The single molecule reagent according to claim 40, wherein the compound containing hydrogen bonding atoms comprises a member selected from the group consisting of ethers and thioethers.

42.-54. (Withdrawn)

55. (Currently Amended) The single molecule reagent according to claim 33, wherein the effector agent is coupled to the trifunctional cross-linking moiety by the second linker which comprises a spacer having a length of 1-25 atoms ~~or groups of atoms~~.

56. (Currently Amended) The single molecule reagent according to claim 33, wherein the effector agent is coupled to the trifunctional cross-linking moiety by the second linker which comprises a spacer having a length of 6-18 atoms, ~~or groups of atoms~~.

57. (Previously Added) The single molecule reagent according to claim 33, wherein the second linker aids in water solubility.

58. (Previously Added) The single molecule reagent according to claim 57, wherein the second linker comprises a hydrogen-bonding atom.

59. (Previously Added) The single molecule reagent according to claim 58 wherein the second linker comprises ethers or thioethers.

60.-61. (Withdrawn)

62. (Previously Added) The single molecule reagent according to claim 33, wherein the biomolecule reactive moiety comprises a member selected from the group consisting of an active ester; an N-hydroxy-succinimide ester; a sulfo-N-hydroxysuccinimide ester; a phenolic ester; an

aryl imidate; an alkyl imidate; an alkyl isocyanate, an aryl isocyanate or an isothiocyanate which reacts with one or more amino groups on the biomolecule; a maleimide, or an alpha-haloamide which reacts with one or more sulfhydryl groups on the biomolecule; and an arylhydrazine, an alkylhydrazine, an alkyl hydroxylamine or an aryl hydroxylamine which reacts with one or more aldehyde or ketone groups either naturally occurring or synthetically produced on the biomolecule.

63. (Withdrawn)

64. (Currently Amended) The single molecule reagent according to claim 33, wherein the biomolecule reactive moiety is coupled to the trifunctional cross-linking moiety with a third linker comprising a spacer having a length of 1-25 atoms, ~~or groups of atoms~~.

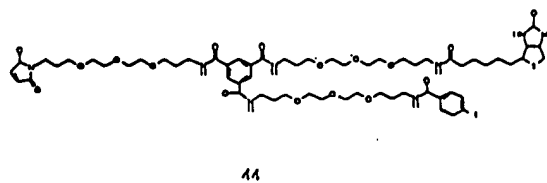
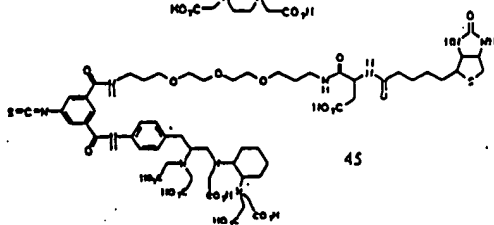
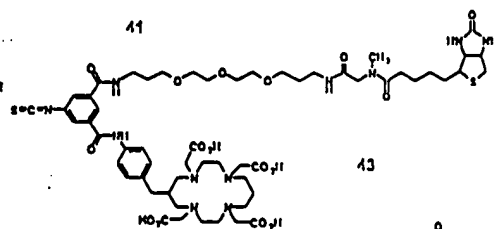
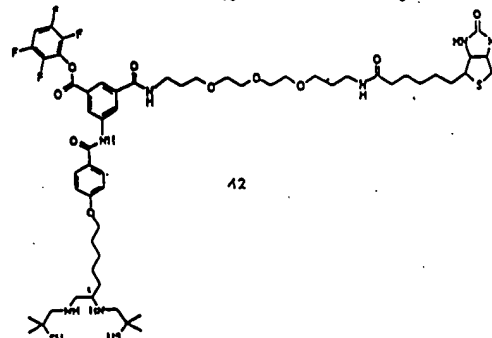
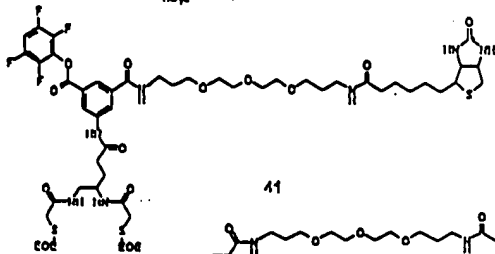
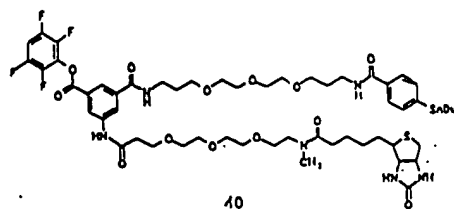
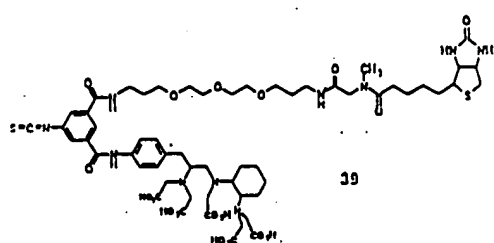
65. (Currently Amended) The single molecule reagent according to claim 33, wherein the biomolecule reactive moiety is coupled to the trifunctional cross-linking moiety with a third linker comprising a spacer having a length of 6-18 atoms, ~~or groups of atoms~~.

66. (Previously Added) The single molecule reagent according to claim 33, wherein the third linker comprises at least one hydrogen- bonding atom.

67. (Previously Added) The single molecule reagent according to claim 66, wherein the hydrogen-bonding atom comprises a member selected from the group consisting of ethers and thioethers.

68. -69. (Withdrawn)

70. (Currently Amended) The single molecule reagent according to claim 33, wherein the reagent is a member selected from the group consisting of the following compounds:



71.-72. (Withdrawn)

73. (Previously Added) A reagent for the diagnosis of a condition or disease in a mammal, the condition or disease selected from the group consisting of cancer, myocardial infarction, deep vein thrombosis, stroke loci, pulmonary embolism and atherosclerosis, the reagent comprising the single molecule reagent according to claim 33.

74. (Previously Added) A reagent for the treatment of a condition or disease in a mammal, the condition or disease selected from the group consisting of cancer, myocardial infarction, deep vein thrombosis, stroke loci, pulmonary embolism and atherosclerosis, the reagent comprising the single molecule reagent according to claim 33.

75.-87 (Withdrawn)

88. (Currently Amended) A diagnostic or therapeutic conjugate which can be extracorporeally eliminated from the blood of a mammal to which it is administered to minimize undesired toxic side-effects, the conjugate comprising:

~~an optionally modified a biomolecule, having a desired biological property retained;~~ and

the single molecule reagent according to claim 33, having at least one affinity ligand and at least one effector agent bound to the reagent.

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Amendment  
Docket No. 033700.005

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89. (Currently Amended) A method of making a diagnostic or therapeutic conjugate which can be extracorporeally eliminated from the blood of a mammal to which it is administered to minimize undesired toxic side-effects, the method comprising reacting:

~~an optionally modified a biomolecule, having a desired biological property~~  
~~retained;~~ and

the single molecule reagent according to claim 33, having at least one affinity ligand bound and at least one effector agent bound to the reagent.

90.-97. (Withdrawn)